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TABLETS
TONOCARD®
(tocainide HCl)

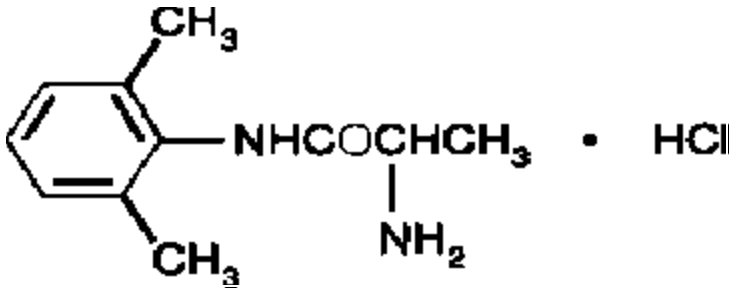
WARNINGS

Blood Dyscrasias: Agranulocytosis, bone marrow depression, leukopenia, neutropenia, aplastic/hypoplastic anemia, thrombocytopenia and sequelae such as septicemia and septic shock have been reported in patients receiving TONOCARD. Most of these patients received TONOCARD within the recommended dosage range. Fatalities have occurred (with approximately 25% mortality in reported agranulocytosis cases). Since most of these events have been noted during the first 12 weeks of therapy, it is recommended that complete blood counts, including white cell, differential and platelet counts be performed, optimally, at weekly intervals for the first 3 months of therapy; and frequently thereafter. Complete blood counts should be performed promptly if the patient develops any signs of infection (such as fever, chills, sore throat, or stomatitis), bruising, or bleeding. If any of these hematologic disorders is identified, TONOCARD should be discontinued and appropriate treatment should be instituted if necessary. Blood counts usually return to normal within 1 month of discontinuation. Caution should be used in patients with pre-existing marrow failure or cytopenia of any type. (See ADVERSE REACTIONS.)

Pulmonary Fibrosis: Pulmonary fibrosis, interstitial pneumonitis, fibrosing alveolitis, pulmonary edema, and pneumonia have been reported in patients receiving TONOCARD. Many of these events occurred in patients who were seriously ill. Fatalities have been reported. The experiences are usually characterized by bilateral infiltrates on x-ray and are frequently associated with dyspnea and cough. Fever may or may not be present. Patients should be instructed to promptly report the development of any pulmonary symptoms such as exertional dyspnea, cough or wheezing. Chest x-rays are advisable at that time. If these pulmonary disorders develop, TONOCARD should be discontinued. (See ADVERSE REACTIONS.)

DESCRIPTION

TONOCARD* (tocainide HCl) is a primary amine analog of lidocaine with antiarrhythmic properties useful in the treatment of ventricular arrhythmias. The chemical name for tocainide hydrochloride is 2-amino-*N*-(2,6-dimethylphenyl) propanamide hydrochloride. Its empirical formula is $C_{11}H_{16}N_2O$•HCl, with a molecular weight of 228.72. The structural formula is



Tocainide hydrochloride is a white crystalline powder with a bitter taste and is freely soluble in water. It is supplied as 400 mg and 600 mg tablets for oral administration. Each tablet contains the following inactive ingredients: hydroxypropyl methylcellulose, iron oxide, magnesium stearate, methylcellulose, polyethylene glycol, and titanium dioxide.

CLINICAL PHARMACOLOGY

Action

Tocainide, like lidocaine, produces dose dependent decreases in sodium and potassium conductance, thereby decreasing the excitability of myocardial cells. In experimental animal models, the dose-related depression of sodium current is more pronounced in ischemic tissue than in normal tissue.

Electrophysiology

Tocainide is a Class I antiarrhythmic compound with electrophysiologic properties in man similar to those of lidocaine, but dissimilar from quinidine, procainamide, and disopyramide.

In studies of isolated dog Purkinje fibers, tocainide in concentrations of 1-50 mcg/mL had no significant effect on resting membrane potential, but reduced the amplitude and rate of depolarization (dv/dt) of the action potential. Tocainide decreased the effective refractory period (ERP) to a lesser extent than the action potential duration (APD) resulting in an increase in the ERP/APD ratio.

In patients with cardiac disease, TONOCARD produced no clinically significant changes in sinus nodal function, effective refractory periods, or intracardiac conduction times when studied under electrophysiologic testing procedures.

Tocainide, like lidocaine, characteristically does not prolong ventricular depolarization (QRS duration) or repolarization (QT intervals) as measured by electrocardiography. Theoretically, therefore, TONOCARD may be useful in the treatment of ventricular arrhythmias associated with a prolonged QT interval.

Patients who respond to lidocaine also respond to TONOCARD in a majority of cases. Failure to respond to lidocaine usually predicts failure to respond to TONOCARD, but there are exceptions to this.

In a controlled comparison with quinidine, 600 mg b.i.d. of TONOCARD produced a mean reduction of 42% in PVC count, compared to a 54% reduction by quinidine 300 mg every 6 hours. Among all patients entered into the study, about one-fifth of tocainide recipients and one-third of quinidine recipients had 75% or greater reductions in PVC count or had elimination of ventricular tachycardia.

Pharmacokinetics

Following oral administration of tocainide, peak plasma concentrations occur within 0.5 to 2 hours. The average plasma half-life in patients is approximately 15 hours. Although the effective plasma concentration may vary from patient to patient, the usual therapeutic plasma range (as defined by 50-80% PVC suppression) is 4-10 mcg/mL (18-45 micromole/L), expressed as tocainide hydrochloride. Tocainide is approximately 10% bound to plasma protein.

In contrast to lidocaine, tocainide undergoes negligible first pass hepatic degradation. Following oral administration, the bioavailability of TONOCARD approaches 100%. The extent of its bioavailability is unaffected by food. Tocainide has no cardioactive metabolites. Approximately 40% of the administered dose of tocainide is excreted unchanged in the urine. Acidification of the urine has not been shown to significantly alter tocainide excretion in the urine, but alkalinization of the urine results in a significant decrease in the percent of tocainide excreted unchanged in the urine. Animal data indicate that tocainide crosses the blood-brain barrier; however, it has less lipid solubility than lidocaine.

Hemodynamics

Cardiac catheterization studies in man utilizing intravenous tocainide infusions (0.5-0.75 mg/kg/min over 15 min) have shown that tocainide usually produces a small degree of depression of parameters of left ventricular function, such as left ventricular dP/dt, and left ventricular end diastolic pressure. There were usually no changes in cardiac output or clinical evidence of increasing congestive heart failure in the well-compensated patients studied. Small but statistically significant increases in aortic and pulmonary arterial pressures have been consistently observed and are probably related to small increases in vascular resistance. When used concomitantly with a beta-blocking drug, tocainide further reduced cardiac index and left ventricular dP/dt and further increased pulmonary wedge pressure.

No clinically significant changes in heart rate, blood pressure, or signs of myocardial depression were observed in a study of 72 post-myocardial infarction patients receiving long-term therapy with oral TONOCARD at usual doses (400 mg q8h). When tocainide was administered orally at a dose of 120 mg/kg to anesthetized dogs (14 times the initial maximum dose recommended for humans), a negative inotropic effect was observed: the rate of change of left ventricular pressure decreased by up to 29% of control at 3 hours after administration. This effect was not observed at lower doses (60 mg/kg). Tocainide has been used safely in patients with acute myocardial infarction and various degrees of congestive heart failure. It has, however, a small negative inotropic effect and can increase peripheral resistance slightly. It therefore should be used cautiously in patients with known heart failure, particularly if a beta blocker is given as well. (See PRECAUTIONS.)

INDICATIONS AND USAGE

TONOCARD is indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that, in the judgment of the physician, are life-threatening. Because of the proarrhythmic effects of TONOCARD, as well as its potential for other serious adverse effects, (see WARNINGS), its use to treat lesser arrhythmias is not recommended. Treatment of patients with asymptomatic ventricular premature contractions should be avoided.

Initiation of treatment with TONOCARD, as with other antiarrhythmic agents used to treat life-threatening arrhythmias, should be carried out in the hospital. It is essential that each patient given TONOCARD be evaluated electrocardiographically and clinically prior to, and during, therapy with TONOCARD to determine whether the response to TONOCARD supports continued treatment.

Antiarrhythmic drugs have not been shown to enhance survival in patients with ventricular arrhythmias.

CONTRAINDICATIONS

Patients who are hypersensitive to this product or to local anesthetics of the amide type.

Patients with second or third degree atrioventricular block in the absence of an artificial ventricular pacemaker.

WARNINGS

Mortality: **In the National Heart, Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multi-center, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had a myocardial infarction more than 6 days but less than 2 years previously, an excessive mortality or non-fatal cardiac arrest rate (7.7%) was seen in patients treated with encainide or flecainide compared with that seen in patients assigned to carefully matched placebo-treated groups (3.0%). The average duration of treatment with encainide or flecainide in this study was 10 months.**

The applicability of the CAST results to other populations (e.g., those without recent myocardial infarction) is uncertain. Considering the known proarrhythmic properties of TONOCARD (tocainide HCl) and the lack of evidence of improved survival for any antiarrhythmic drug in patients without life-threatening arrhythmias, the use of TONOCARD as well as other antiarrhythmic agents should be reserved for patients with life-threatening ventricular arrhythmias.

Acceleration of Ventricular Rate: Acceleration of ventricular rate occurs infrequently when antiarrhythmics are administered to patients with atrial flutter or fibrillation (see ADVERSE REACTIONS).

PRECAUTIONS

General

In patients with known heart failure or minimal cardiac reserve, TONOCARD should be used with caution because of the potential for aggravating the degree of heart failure.

Caution should be used in the institution or continuation of antiarrhythmic therapy in the presence of signs of increasing depression of cardiac conductivity.

In patients with severe liver or kidney disease, the rate of drug elimination may be significantly decreased (see DOSAGE AND ADMINISTRATION).

Since antiarrhythmic drugs may be ineffective in patients with hypokalemia, the possibility of a potassium deficit should be explored and, if present, the deficit should be corrected.

Like all other oral antiarrhythmics, TONOCARD has been reported to increase arrhythmias in some patients (see ADVERSE REACTIONS).

Information for Patients

Patients should be instructed to promptly report the development of bruising or bleeding; any signs of infections such as fever, chills, sore throat, or soreness and ulcers in the mouth; any pulmonary symptoms, such as exertional dyspnea, cough, or wheezing; rash.

Laboratory Tests

As with other antiarrhythmics, abnormal liver function tests, particularly in the early stages of therapy, have been reported. Periodic monitoring of liver function should be considered. Hepatitis and jaundice have been reported in some patients.

Drug Interactions

Tocainide and lidocaine are pharmacodynamically similar. The concomitant use of these 2 agents may cause an increased incidence of adverse reactions, including central nervous system adverse reactions such as seizure.

Specific interaction studies with cimetidine, digoxin, metoprolol and warfarin have been conducted, no clinically significant interaction was seen with cimetidine, digoxin or warfarin; but tocainide and metoprolol had additive effects on wedge pressure and cardiac index. TONOCARD has also been used in open studies with digitalis, beta-blocking agents, other antiarrhythmic agents, anticoagulants, and diuretics, without evidence of clinically significant interactions. Nevertheless, caution should be exercised in the use of multiple drug therapy.

TONOCARD is equally effective in digitalized and nondigitalized patients. In 17 patients with refractory ventricular arrhythmias on concomitant therapy, serum digoxin levels (1.1 ± 0.4 ng/mL) remained in the expected normal range (0.5-2.5 ng/mL) during tocainide administration.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of tocainide was studied in mice using oral doses up to 300 mg/kg/day (about 6 times the maximum recommended human dose) for up to 94 weeks in males and 102 weeks in females and in rats at doses up to 200 mg/kg/day for 24 months. Tocainide did not affect the type or incidence of neoplasia in the 2 studies.

Tocainide did not show any mutagenic potential when evaluated *in vivo* in the micronucleus test using mice at oral doses up to 187.5 mg/kg/day (about 7 times the usual human dose). Also, no mutagenic activity was seen *in vitro* in the Ames microbial mutagen test or in the mouse lymphoma forward mutation assay.

Reproduction and fertility studies in rats showed no adverse effects on male or female fertility at oral doses up to 200 mg/kg/day (about 8 times the usual human dose).

Pregnancy

Pregnancy Category C. In a teratogenicity study in rabbits, tocainide was administered orally at doses of 25, 50, and 100 mg/kg/day (about 1 to 4 times the usual human dose). No evidence of a drug-related teratogenic effect was noted; however, these doses were maternotoxic and produced a dose-related increase in abortions and stillbirths. In a teratogenicity study in rats, an oral dose of 300 mg/kg/day (about 12 times the usual human dose) showed no evidence of treatment-related fetal malformations, but maternotoxicity and an increase in fetal resorptions were noted. An oral dose of 30 mg/kg/day (about twice the usual human dose) did not produce any adverse effects.

In reproduction studies in rats at maternotoxic oral doses of 200 and 300 mg/kg/day (about 8 and 12 times the usual human dose, respectively), dystocia, and delayed parturition occurred which was accompanied by an increase in stillbirths and decreased survival in offspring during the first week postpartum. Growth and viability of surviving offspring were not affected for the remainder of the lactation period.

There are no adequate and well-controlled studies in pregnant women. TONOCARD should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Tocainide is secreted in human milk. Because of the potential for serious adverse reactions in nursing infants from TONOCARD, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of TONOCARD did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

TONOCARD commonly produces minor, transient, nervous system and gastrointestinal adverse reactions, but is otherwise generally well tolerated. TONOCARD has been evaluated in both short-term (n = 1,358) and long-term (n = 262) controlled studies as well as a compassionate use program. Dosages were lower in most of the controlled studies (1200 mg/day) and higher in the compassionate use program (1800 mg and more). In long-term (2-6 months) controlled studies, the most frequent adverse reactions were dizziness/vertigo (15.3%), nausea (14.5%), paresthesia (9.2%), and tremor (8.4%). These reactions were generally mild, transient, dose-related and reversible with a reduction in dosage, by taking the drug with food, or by therapy discontinuation. Tremor, when present, may be useful as a clinical indicator that the maximum dose is being approached. Adverse reactions leading to therapy discontinuation occurred in 21% of patients in long-term controlled trials and were usually related to the nervous system or digestive system.

Adverse reactions occurring in greater than 1% of patients from the short-term and long-term controlled studies appear in the following table:

	Percent of Patients Controlled Studies	
	Short-term (n = 1,358)	Long-term (n = 262)
BODY AS A WHOLE		
Tiredness/drowsiness/fatigue/ lethargy/lassitude/sleepiness	1.6	0.8
Hot/cold feelings	0.5	1.5
CARDIOVASCULAR		
Hypotension	3.4	2.7
Bradycardia	1.8	0.4
Palpitations	1.8	0.4
Chest pain	1.6	0.4
Conduction disorders	1.5	0.0
Left ventricular failure	1.4	0.0
DIGESTIVE		
Nausea	15.2	14.5
Vomiting	8.3	4.6
Anorexia	1.2	1.9
Diarrhea/loose stools	0.0	3.8
NERVOUS SYSTEM/PSYCHIATRIC		
Dizziness/vertigo	8.0	15.3
Paresthesia	3.5	9.2
Tremor	2.9	8.4
Confusion/disorientation/ hallucinations	2.1	2.7
Headache	2.1	4.6
Nervousness	1.5	0.4
Altered mood/awareness	1.5	3.4
Incoordination/unsteadiness/ walking disturbances	1.2	0.0
Anxiety	1.1	1.5
Ataxia	0.2	3.0
SKIN		
Diaphoresis	5.1	2.3
Rash/skin lesion	0.4	8.4
SPECIAL SENSES		
Blurred vision/visual disturbances	1.3	1.5
Tinnitus/hearing loss	0.4	1.5
Nystagmus	0.0	1.1

An additional group of about 2,000 patients has been treated in a program allowing for the use of TONOCARD under compassionate use circumstances. These patients were seriously ill with the large majority on multiple drug therapy, and comparatively high doses of TONOCARD were used. Fifty-four percent of the patients continued in the program for 1 year or longer, and 12% were treated for longer than 3 years, with the

longest duration of therapy being 9 years. Adverse reactions leading to therapy discontinuation occurred in 12% of patients (usually central nervous system effects or rash). A tabulation of adverse reactions occurring in 1% or more of patients follows:

	Percent of Patients Compassionate Use (n = 1,927)
CARDIOVASCULAR	
Increased ventricular arrhythmias/PVCs	10.9
CHF/progression of CHF	4.0
Tachycardia	3.2
Hypotension	1.8
Conduction disorders	1.3
Bradycardia	1.0
DIGESTIVE	
Nausea	24.6
Anorexia	11.3
Vomiting	9.0
Diarrhea/loose stools	6.8
MUSCULOSKELETAL	
Arthritis/arthralgia	4.7
Myalgia	1.7
NERVOUS SYSTEM/PSYCHIATRIC	
Dizziness/vertigo	25.3
Tremor	21.6
Nervousness	11.5
Confusion/disorientation/hallucinations	11.2
Altered mood/awareness	11.0
Ataxia	10.8
Paresthesia	9.2
SKIN	
Rash/skin lesion	12.2
Diaphoresis	8.3
Lupus	1.6
SPECIAL SENSES	
Blurred vision/vision disturbances	10.0
Nystagmus	1.1

Adverse reactions occurring in less than 1% of patients in either the controlled studies or the compassionate use program or since the drug was marketed are as follows:

Body as a Whole: Septicemia; septic shock; syncope; vasovagal episodes; edema; fever; chills; cinchonism; asthenia; malaise.

Cardiovascular: Ventricular fibrillation; extension of acute myocardial infarction; cardiogenic shock; pulmonary embolism; angina; AV block; hypertension; claudication; increased QRS

duration; pleurisy/pericarditis; prolonged QT interval; right bundle branch block; cardiomegaly; sinus arrest; vasculitis; orthostatic hypotension; cold extremities.

Digestive: Hepatitis, jaundice (see PRECAUTIONS), abnormal liver function tests; pancreatitis; abdominal pain/discomfort; constipation; dysphagia; gastrointestinal symptoms (including dyspepsia); stomatitis; dry mouth; thirst.

Hematologic: Agranulocytosis; bone marrow depression; aplastic/hypoplastic anemia; hemolytic anemia; anemia; leukopenia; neutropenia; thrombocytopenia; eosinophilia.

Metabolic and Immune: Hypersensitivity Reaction (including some of the following symptoms or signs: rash, fever, joint pains, abnormal liver function tests, eosinophilia); increased ANA.

Musculoskeletal: Muscle cramps; muscle twitching/spasm; neck pain; pain radiating from neck; pressure on shoulder.

Nervous System/Psychiatric: Coma; convulsions/seizures; myasthenia gravis; depression; psychosis; psychic disturbances; agitation; decreased mental acuity; dysarthria; impaired memory; increased stuttering/slurred speech; insomnia/sleeping disturbances; local anesthesia; dream abnormalities.

Respiratory: Respiratory arrest; pulmonary edema; pulmonary fibrosis; fibrosing alveolitis; pneumonia; interstitial pneumonitis; dyspnea; hiccough; yawning.

Skin: Stevens-Johnson syndrome; exfoliative dermatitis; erythema multiforme; urticaria; alopecia; pruritus; pallor/flushed face.

Special Senses: Diplopia; earache; taste perversion/smell perversion.

Urogenital: Urinary retention; polyuria/increased diuresis.

Agranulocytosis, bone marrow depression, leukopenia, neutropenia, aplastic/hypoplastic anemia, and thrombocytopenia have been reported (0.18%) in patients receiving TONOCARD in controlled trials and the compassionate use program. Most of these events have been noted during the first 12 weeks of therapy. (See Box WARNINGS.)

Pulmonary fibrosis, interstitial pneumonitis, fibrosing alveolitis, pulmonary edema, and pneumonia, have been reported in patients receiving TONOCARD. The incidence of pulmonary fibrosis (including interstitial pneumonitis and fibrosing alveolitis) was 0.11% in controlled trials and the compassionate use program. These events usually occurred in seriously ill patients. Symptoms of these pulmonary disorders and/or x-ray changes usually occurred following 3-18 weeks of therapy. Fatalities have been reported. (See Box WARNINGS.)

A number of disorders, in which a causal relationship with TONOCARD has not been established, have been reported in seriously ill patients. These include: renal failure, renal dysfunction, myocardial infarction, cerebrovascular accidents and transient ischemic attacks. These disorders may be related to the patient's underlying condition.

DRUG ABUSE AND DEPENDENCE

Drug withdrawal after chronic treatment has not shown any indication of psychological or physical dependence.

OVERDOSAGE

The initial and most important signs and symptoms of overdosage would be expected to be related to the central nervous system. Other adverse reactions, such as gastrointestinal disturbances, may follow. (See ADVERSE REACTIONS.)

Should convulsions or cardiopulmonary depression or arrest develop, the patency of the airway and adequacy of ventilation must be assured immediately. Should convulsions persist despite ventilatory therapy with oxygen, small increments of anticonvulsive agents may be given intravenously. Examples of such agents include a benzodiazepine (eg, diazepam), an ultrashort-acting barbiturate (eg, thiopental or thiamylal), or a short-acting barbiturate (eg, pentobarbital or secobarbital).

The oral LD_{50} of tocainide was calculated to be about 800 mg/kg in mice, 1000 mg/kg in rats, and 230 mg/kg in guinea pigs; deaths were usually preceded by convulsions.

Studies in normal individuals to date indicate that tocainide has a hemodialysis clearance approximately equivalent to its renal clearance.

DOSAGE AND ADMINISTRATION

The dosage of TONOCARD must be individualized on the basis of antiarrhythmic response and tolerance, both of which are dose-related. Clinical and electrocardiographic evaluation (including Holter monitoring if necessary for evaluation) are needed to determine whether the desired antiarrhythmic response has been obtained and to guide titration and dose adjustment. Adverse effects appearing shortly after dosing, for example, suggest a need for dividing the dose further with a shorter dose-interval. Loss of arrhythmia control prior to the next dose suggests use of a shorter dose interval and/or a dose increase. Absence of a clear response suggests reconsideration of therapy.

The recommended initial dosage is 400 mg every 8 hours. The usual adult dosage is between 1200 and 1800 mg/day in a three dose daily divided regimen. Doses beyond 2400 mg per day have been administered infrequently. Patients who tolerate the t.i.d. regimen may be tried on a twice daily regimen with careful monitoring.
Some patients, particularly those with renal or hepatic impairment, may be adequately treated with less than 1200 mg/day.

HOW SUPPLIED

No. 3409 — Tablets TONOCARD, 400 mg, are oval, yellow, scored, film-coated tablets, coded 707 on one side and TONOCARD on the other side. They are supplied as follows:

NDC 0186-0707-68 bottles of 100
No. 3410 — Tablets TONOCARD, 600 mg, are oblong, yellow, scored, film-coated tablets, coded 709 on one side and TONOCARD on the other side. They are supplied as follows:

NDC 0186-0709-68 bottles of 100

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep container tightly closed.

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